7/3/38 (Item 3 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
(c) 2003 American Chemical Society. All rts. reserv.

119026686 CA: 119(3)26686d PATENT
Inhibition of vascular narrowing using anti-PADGEM antibodies
INVENTOR(AUTHOR): Palabrica, Theresa M.; Furie, Bruce E.; Furie, Barbara C.
LOCATION: USA
ASSIGNEE: Biogen, Inc.; New England Medical Center Hospitals, Inc.
PATENT: PCT International ; WO 9306863 A1 DATE: 930415
APPLICATION: WO 92US8163 (920930) *US 768834 (910930)
PAGES: 32 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: A61K-039/395A
DESIGNATED COUNTRIES: AT; AU; BB; BG; BR; CA; CH; CS; DE; DK; ES; FI; GB; HU; JP; KP; KR; LK; LU; MG; MN; MW; NL; NO; PL; RO; RU; SD; SE; US
DESIGNATED REGIONAL: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LU; MC; NL; SE; BF; BJ; CF; CG; CI; CM; GA; GN; ML; MR; SN; TD; TG
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File 410:Chronolog(R)  1981-2002/Nov
       (c) 2002 The Dialog Corporation

      Set  Items  Description
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     $0.00  Estimated cost File410
     $0.03  TELNET
     $0.03  Estimated cost this search
     $0.36  Estimated total session cost   0.164 DialUnits

SYSTEM:OS  - DIALOG OneSearch
  File   5:Biosis Previews(R)  1969-2003/Jan W3
         (c) 2003 BIOSIS
*File   5: Alert feature enhanced for multiple files, duplicates
removal, customized scheduling. See HELP ALERT.
  File  73:EMBASE  1974-2003/Jan W3
         (c) 2003 Elsevier Science B.V.
*File  73: Alert feature enhanced for multiple files, duplicates
removal, customized scheduling. See HELP ALERT.
  File 155:MEDLINE(R)  1966-2003/Jan W3
*File 155: Updating of completed records has resumed.See Help News155.
Alert feature enhanced with customized scheduling. See HELP ALERT.
  File 399:CA SEARCH(R)  1967-2003/UD=13804
         (c) 2003 American Chemical Society
*File 399: Use is subject to the terms of your user/customer agreement.
Alert feature enhanced for multiple files, etc. See HELP ALERT.

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E1         1  AU=WAGNER DENIS D
E2         2  AU=WAGNER DENISA
E3         0 *AU=WAGNER DENISA ?
E4        86  AU=WAGNER DENISA D
E5         2  AU=WAGNER DENNIS L
E6         2  AU=WAGNER DIANA
E7        18  AU=WAGNER DIANE
E8         2  AU=WAGNER DIANE R
E9         1  AU=WAGNER DIAS CASALI, VICENTE
E10        7  AU=WAGNER DIETER
E11       11  AU=WAGNER DIRK
E12        1  AU=WAGNER DJAMILEH

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      S1      89  E1-E4
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         4093439  P
           29273  SELECTIN
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           153621  ATHEROSCLEROSIS
      S4        6  S3 AND ATHEROSCLEROSIS
? rd s4
...completed examining records
      S5        6  RD S4 (unique items)
? t s5/3/all

 5/3/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

13244369   BIOSIS NO.: 200100451518
Localized reduction of atherosclerosis in von Willebrand
  factor-deficient mice.
AUTHOR: Methia Nassia; Andre Patrick; Denis Cecile V; Economopoulos Maria;
  Wagner Denisa D(a
AUTHOR ADDRESS: (a)Center for Blood Research, Harvard Medical School, 800
  Huntington Ave, Boston, MA, 02115: wagner@cbr.med.harvard.edu**USA
JOURNAL: Blood  98 (5):p1424-1428 September 1, 2001
MEDIUM: print
ISSN: 0006-4971
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English


 5/3/2     (Item 2 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

12558541   BIOSIS NO.: 200000312043
Prominent role of P-selectin in the development of advanced
  atherosclerosis in apoE-deficient mice.
AUTHOR: Dong Zhao Ming; Brown Allison A; Wagner Denisa D
AUTHOR ADDRESS: (a)Center for Blood Research, Harvard Medical School, 800
  Huntington Ave, Boston, MA, 02115**USA
JOURNAL: Circulation  101 (19):p2290-2295 May 16, 2000
MEDIUM: print
ISSN: 0009-7322
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English


 5/3/3     (Item 3 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

12247464   BIOSIS NO.: 200000000966
New discoveries with mice mutant in endothelial and platelet selectins.
AUTHOR: Hartwell Daqing W; Wagner Denisa D(a
AUTHOR ADDRESS: (a)Center for Blood Research, Harvard Medical School, 800
  Huntington Avenue, Boston, MA**USA
JOURNAL: Thrombosis and Haemostasis  82 (2):p850-857 Aug., 1999
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ISSN: 0340-6245
DOCUMENT TYPE: Literature Review
RECORD TYPE: Citation
LANGUAGE: English

5/3/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

11577140 BIOSIS NO.: 199800357836
The combined role of P- and E-selectins in **atherosclerosis**.
AUTHOR: Dong Zhao Ming; Chapman Susan M; Brown Allison A; Frenette Paul S; Hynes Richard O; **Wagner Denisa D**(a
AUTHOR ADDRESS: (a)Cent. Blood Res., Harvard Med. Sch., 800 Huntington Avenue, Boston, MA 02115**USA
JOURNAL: Journal of Clinical Investigation 102 (1):p145-152 July 1, 1998
ISSN: 0021-9738
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

5/3/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

10846658 BIOSIS NO.: 199799467803
Absence of **P-selectin** delays fatty streak formation in mice.
AUTHOR: Johnson Robert C; Chapman Susan M; Dong Zaho Ming; Ordovas Jose M; Mayadas Tanya N; Herz Joachim; Hynes Richard O; Schaefer Ernest J; **Wagner Denisa D**(a
AUTHOR ADDRESS: (a)Center Blood Research, Harvard Med. Sch., 800 Huntington Ave., Boston, MA 02115**USA
JOURNAL: Journal of Clinical Investigation 99 (5):p1037-1043 1997
ISSN: 0021-9738
RECORD TYPE: Abstract
LANGUAGE: English

5/3/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

10163013 BIOSIS NO.: 199698617931
P-selectin knockout: A mouse model for various human diseases.
BOOK TITLE: Ciba Foundation Symposium; Cell adhesion and human disease
AUTHOR: **Wagner Denisa D**
BOOK AUTHOR/EDITOR: Marsh J; Goode J A: Eds
AUTHOR ADDRESS: Cent. Blood Res., Harvard Med. Sch., 800 Huntington Avenue, Boston, MA 02115**USA
JOURNAL: Ciba Foundation Symposium (198):p2-16 1995
BOOK PUBLISHER: John Wiley and Sons Ltd., Baffin Lane, Chichester PO 19 1UD, England
John Wiley and Sons, Inc., 605 Third Avenue, New York, New York 10158-0012, USA
CONFERENCE/MEETING: Symposium London, England, UK May 17-19, 1994
ISSN: 0300-5208 ISBN: 0-471-95279-6
RECORD TYPE: Citation
LANGUAGE: English
? s (p(w)selectin or gmp(w)140 or padgem?)(20n)(antibod?) and atherosclerosis
4093439 P
29273 SELECTIN
11027 P(W)SELECTIN

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          69871  GMP
          91378  140
            954  GMP(W)140
           3426  PADGEM?
        1770659  ANTIBOD?
           2517  ((P(W)SELECTIN OR GMP(W)140) OR PADGEM?)(20N)ANTIBOD?
         153621  ATHEROSCLEROSIS
      S6      64  (P(W)SELECTIN OR GMP(W)140 OR PADGEM?)(20N)(ANTIBOD?) AND
                  ATHEROSCLEROSIS
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...examined 50 records  (50)
...completed examining records
      S7      38  RD S6 (unique items)
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 7/3/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

13889124   BIOSIS NO.: 200200517945
Deposition of platelet RANTES triggering monocyte recruitment requires
  P-selectin and is involved in neointima formation after arterial injury.
AUTHOR: Schober Andreas; Manka David; von Hundelshausen Philipp; Huo Yuqing
  ; Hanrath Peter; Sarembock Ian J; Ley Klaus; Weber Christian(a)
AUTHOR ADDRESS: (a)Kardiovaskulaere Molekularbiologie,
  Universitaetsklinikum Aachen, Pauwelsstrasse 30, 52074, Aachen**Germany
  E-Mail: cweber@ukaachen.de
JOURNAL: Circulation  106 (12):p1523-1529 September 17, 2002
MEDIUM: print
ISSN: 0009-7322
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English


 7/3/2     (Item 2 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

13345239   BIOSIS NO.: 200100552388
High-shear-stress-induced activation of platelets and microparticles
  enhances expression of cell adhesion molecules in THP-1 and endothelial
  cells.
AUTHOR: Nomura Shosaku(a); Tandon Narendra N; Nakamura Takashi; Cone James;
  Fukuhara Shirou; Kambayashi Junichi
AUTHOR ADDRESS: (a)Otsuka America Pharmaceutical Inc., Rockville, MD,
  20850: fwkg4681@mb.infoweb.ne.jp**USA
JOURNAL: Atherosclerosis  158 (2):p277-287 October, 2001
MEDIUM: print
ISSN: 0021-9150
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English


 7/3/3     (Item 3 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

13329489   BIOSIS NO.: 200100536638
Adhesion molecules and atherogenesis.
AUTHOR: Huo Y; Ley K(a)
AUTHOR ADDRESS: (a)Department of Biomedical Engineering, Health Science
```

Center, University of Virginia, Charlottesville, VA, 22908**USA
JOURNAL: Acta Physiologica Scandinavica 173 (1):p35-43 September, 2001
MEDIUM: print
ISSN: 0001-6772
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

7/3/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

13068220 BIOSIS NO.: 200100275369
Cholesterol sulfate: A new adhesive molecule for platelets.
AUTHOR: Merten Michael; Dong Jing Fei; Lopez Jose A; Thiagarajan Perumal(a)
AUTHOR ADDRESS: (a)University of Texas at Houston Medical School, 6431 Fannin, MSB 5.284, Houston, TX, 77030: Perumal.Thiagarajan@uth.tmc.edu** USA
JOURNAL: Circulation 103 (16):p2032-2034 April 24, 2001
MEDIUM: print
ISSN: 0009-7322
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

7/3/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

13064423 BIOSIS NO.: 200100271572
Direct viewing of **atherosclerosis** in vivo: Plaque invasion by leukocytes is initiated by the endothelial selectins.
AUTHOR: Eriksson Einar E(a); Xie Xun; Werr Joachim; Thoren Peter; Lindbom Lennart
AUTHOR ADDRESS: (a)Department of Physiology and Pharmacology, Karolinska Institutet, S-171 77, Stockholm: einar.eriksson@fyfa.ki.se**Sweden
JOURNAL: FASEB Journal 15 (7):p1149-1157 May, 2001
MEDIUM: print
ISSN: 0892-6638
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

7/3/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

12769681 BIOSIS NO.: 200000523304
Angiotensin II induces leukocyte-endothelial cell interactions in vivo via AT1 and AT2 receptor-mediated P-selectin upregulation.
AUTHOR: Piqueras Laura; Kubes Paul; Alvarez Angeles; O'Connor Enrique; Issekutz Andrew C; Esplugues Juan V; Sanz Maria-Jesus(a)
AUTHOR ADDRESS: (a)Departamento de Farmacologia, Facultad de Medicina, Av. Blasco Ibanez, 15-17, 46010, Valencia**Spain
JOURNAL: Circulation 102 (17):p2118-2123 October 24, 2000
MEDIUM: print
ISSN: 0009-7322
DOCUMENT TYPE: Article

RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

7/3/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

12748146 BIOSIS NO.: 200000501769
Roles of P-selectin in inflammation, neointimal formation, and vascular remodeling in balloon-injured rat carotid arteries.
AUTHOR: Hayashi Shin-ichiro; Watanabe Noboru; Nakazawa Koh; Suzuki Junichi; Tsushima Kenji; Tamatani Takuya; Sakamoto Shinji; Isobe Mitsuaki(a)
AUTHOR ADDRESS: (a)Department of Cardiovascular Medicine, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo, 113-8519**Japan
JOURNAL: Circulation 102 (14):p1710-1717 October 3, 2000
MEDIUM: print
ISSN: 0009-7322
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

7/3/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

12301654 BIOSIS NO.: 200000059521
Endothelin-1 causes P-selectin-dependent leukocyte rolling and adhesion within rat mesenteric microvessels.
AUTHOR: Sanz Maria-Jesus(a); Johnston Brent; Issekutz Andrew; Kubes Paul
AUTHOR ADDRESS: (a)Departamento de Farmacologia, Facultat de Medicina, Universitat de Valencia, Av. Blasco Ibanez, 15-17, 46010, Valencia**Spain
JOURNAL: American Journal of Physiology 277 (5 PART 2):pH1823-H1830 Nov., 1999
ISSN: 0002-9513
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

7/3/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12058582 BIOSIS NO.: 199900339101
Direct demonstration of P-selectin- and VCAM-1-dependent mononuclear cell rolling in early atherosclerotic lesions of apolipoprotein E-deficient mice.
AUTHOR: Ramos Carroll L; Huo Yuqing; Jung Unsu; Ghosh Shukti; Manka David R ; Sarembock Ian J; Ley Klaus(a)
AUTHOR ADDRESS: (a)Department of Biomedical Engineering, Health Sciences Center, University of Virginia, Charlottes**USA
JOURNAL: Circulation Research 84 (11):p1237-1244 June 11, 1999
ISSN: 0009-7330
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

7/3/10 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

11937817 BIOSIS NO.: 199900183926
Enzymatically modified, nonoxidized LDL induces selective adhesion and transmigration of monocytes and T-lymphocytes through human endothelial cell monolayers.
AUTHOR: Klouche Mariam(a); May Andreas E; Hemmes Monika; Messner Martina; Kanse Sandip M; Preissner Klaus T; Bhakdi Sucharit
AUTHOR ADDRESS: (a)Institute of Medical Microbiology, Johannes-Gutenberg University of Mainz, Obere Zahlbacher Stra**Germany
JOURNAL: Arteriosclerosis Thrombosis and Vascular Biology 19 (3):p784-793 March, 1999
ISSN: 1079-5642
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

7/3/11 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

11486174 BIOSIS NO.: 199800267506
Adhesion of monocytes to vascular cell adhesion molecule-1-transduced human endothelial cells. Implications for atherogenesis.
AUTHOR: Gerszten Robert E; Lim Yaw-Chyn; Ding Han T; Snapp Karen; Kansas Goeffrey; Dichek David A; Cabanas Carlos; Sanchez-Madrid Francisco; Gimbrone Michael A Jr; Rosenzweig Anthony; Luscinskas Francis W(a)
AUTHOR ADDRESS: (a)Vascular Res. Div., Brigham and Women's Hosp., 221 Longwood Avenue, Boston, MA 02115**USA
JOURNAL: Circulation Research 82 (8):p871-878 May 4, 1998
ISSN: 0009-7330
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

7/3/12 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

10923857 BIOSIS NO.: 199799545002
Cytokine-induced leukocyte rolling in mouse cremaster muscle arterioles is P-selectin dependent.
AUTHOR: Thorlacius Henrik(a); Lindbom Lennart; Raud Johan
AUTHOR ADDRESS: (a)Dep. Physiol. Pharmacol., Division Physiol. 1, Karolinska Inst., Doktorsringen 6A, S-171 77 Stoc**Sweden
JOURNAL: American Journal of Physiology 272 (4 PART 2):pH1725-H1729 1997
ISSN: 0002-9513
RECORD TYPE: Abstract
LANGUAGE: English

7/3/13 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

10847096 BIOSIS NO.: 199799468241
Molecular determinants of oxidized low-density lipoprotein-induced leukocyte adhesion and microvascular dysfunction.
AUTHOR: Liao Lianxi; Starzyk Ruth M; Granger D Neil(a)
AUTHOR ADDRESS: (a)Dep. Physiol. Biophysics, LSU Med. Center, 1501 Kings

Hwy, PO Box 33932, Shreveport, LA 71130-39**USA
JOURNAL: Arteriosclerosis Thrombosis and Vascular Biology 17 (3):p437-444 1997
ISSN: 1079-5642
RECORD TYPE: Abstract
LANGUAGE: English

7/3/14 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

10709957 BIOSIS NO.: 199799331102
Adhesion of memory lymphocytes to vascular cell adhesion molecule-1-transduced human vascular endothelial cells under simulated physiological flow conditions in vitro.
AUTHOR: Gerszten Robert E; Luscinskas Francis W; Ding Han T; Dichek David A ; Stoolman Lloyd M; Gimbrone Michael A Jr; Rosenzweig Anthony
AUTHOR ADDRESS: Massachusetts Gen. Hosp., Cardiovascular Res. Cent., Mailcode 1494201, 149 13th St., Charlestown, MA**USA
JOURNAL: Circulation Research 79 (6):p1205-1215 1996
ISSN: 0009-7330
RECORD TYPE: Abstract
LANGUAGE: English

7/3/15 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

10477820 BIOSIS NO.: 199699098965
Localized adhesion of monocytes to human atherosclerotic plaques demonstrated in vitro: Implications for atherogenesis.
AUTHOR: Poston Robin N(a); Johnson-Tidey Ruth R
AUTHOR ADDRESS: (a)Dep. Experimental Pathol., UMDS, Guy's Hosp., London SE1 9RT**UK
JOURNAL: American Journal of Pathology 149 (1):p73-80 1996
ISSN: 0002-9440
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

7/3/16 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

10149220 BIOSIS NO.: 199698604138
Shear-induced platelet aggregation in normal subjects and stroke patients.
AUTHOR: Konstantopoulos Konstantinos(a); Grotta James C; Sills Cynthia; Wu Kenneth K; Hellums J David
AUTHOR ADDRESS: (a)Cox Lab. Biomed. Eng., Rice Univ., Houston, TX 77251-1892**USA
JOURNAL: Thrombosis and Haemostasis 74 (5):p1329-1334 1995
ISSN: 0340-6245
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

7/3/17 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

10104062 BIOSIS NO.: 199698558980
Oxidized low-density lipoproteins facilitate leukocyte adhesion to aortic intima without affecting endothelium-dependent relaxation: Role of P-selectin.
AUTHOR: Mehta Asha; Yang Baichun; Khan Saeed; Hendricks James B; Stephen Claudia; Mehta Jawahar L(a)
AUTHOR ADDRESS: (a)Box 100277, JHMHC, Univ. Florida, Gainesville, FL 32610 **USA
JOURNAL: Arteriosclerosis Thrombosis and Vascular Biology 15 (11):p 2076-2083 1995
ISSN: 1079-5642
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

7/3/18 (Item 18 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

09725932 BIOSIS NO.: 199598180850
Flow cytometric studies of platelet responses to shear stress in whole blood.
AUTHOR: Konstantopoulos K(a); Wu K K; Udden M M; Banez E I; Shattil S J; Hellums J D(a)
AUTHOR ADDRESS: (a)Cox Lab. Biomed. Eng., Rice Univ., Houston, TX 77251-1892**USA
JOURNAL: Biorheology 32 (1):p73-93 1995
ISSN: 0006-355X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

7/3/19 (Item 19 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

08944601 BIOSIS NO.: 199396096102
Detection of plasma alpha-granule membrane protein **GMP-140** using radiolabeled monoclonal **antibodies** in thrombotic diseases.
AUTHOR: Wu Guoxin; Li Fugang; Li Peixia; Ruan Changgeng(a)
AUTHOR ADDRESS: (a)Jiangsu Inst. Hematol., Thrombosis and Hemostasis Res. Unit, Suzhou Med. Coll., Suzhou 215007**China
JOURNAL: Haemostasis 23 (2):p121-128 1993
ISSN: 0301-0147
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

7/3/20 (Item 20 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

08896737 BIOSIS NO.: 199396048238
Inhibition of nitric oxide production: Mechanisms of vascular albumin leakage.
AUTHOR: Kurose Iwao; Kubes Paul; Wolf Robert; Anderson Donald C; Paulson James; Miyasaka Masayuki; Granger D Neil(a)
AUTHOR ADDRESS: (a)Dep. Physiology, Louisiana State Univ. Med. Cent., 1501 Kings Highway, PO Box 33932, Shreveport,**USA
JOURNAL: Circulation Research 73 (1):p164-171 1993
ISSN: 0009-7330

DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

7/3/21 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2003 Elsevier Science B.V. All rts. reserv.

11689563 EMBASE No: 2002263152
Flow cytometric assay of platelet glycoprotein receptor numbers in hypercholesterolemia
Ozsavci D.; Yardimci T.; Demirel G.Y.; Demiralp E.; Uras F.; Onder E.
D. Ozsavci, Department of Biochemistry, Marmara Univ. Faculty of Pharmacy, Tibbiye Caddesi, No. 49, Haydarpasa 81010 Kadikoy, Istanbul Turkey
AUTHOR EMAIL: deryaozsavci@hotmail.com
Platelets (PLATELETS) (United Kingdom) 2002, 13/4 (223-229)
CODEN: PLTEE ISSN: 0953-7104
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 37

7/3/22 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2003 Elsevier Science B.V. All rts. reserv.

11686349 EMBASE No: 2002259331
Postprandial lipemia is associated with platelet and monocyte activation and increased monocyte cytokine expression in normolipemic men
Hyson D.A.; Paglieroni T.G.; Wun T.; Rutledge J.C.
Dr. J.C. Rutledge, Department of Internal Medicine, University of California, One Peter Shields Avenue, Davis, CA 95616 United States
AUTHOR EMAIL: jcrutledge@ucdavis.edu
Clinical and Applied Thrombosis/Hemostasis (CLIN. APPL. THROMB. HEMOST.) (United States) 2002, 8/2 (147-155)
CODEN: CATHF ISSN: 1076-0296
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 35

7/3/23 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2003 Elsevier Science B.V. All rts. reserv.

10892929 EMBASE No: 2000374651
Angiotensin II induces leukocyte-endothelial cell interactions in vivo via ATinf 1 and ATinf 2 receptor-mediated P-selectin upregulation
Piqueras L.; Kubes P.; Alvarez A.; O'Connor E.; Issekutz A.C.; Esplugues J.V.; Sanz M.-J.
Dr. M.-J. Sanz, Departamento de Farmacologia, Facultad de Medicina, Av. Blasco Ibanez, 15-17, 46010 Valencia Spain
AUTHOR EMAIL: maria.j.sanz@uv.es
Circulation (CIRCULATION) (United States) 24 OCT 2000, 102/17 (2118-2123)
CODEN: CIRCA ISSN: 0009-7322
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 26

7/3/24 (Item 4 from file: 73)

DIALOG(R)File 73:EMBASE
(c) 2003 Elsevier Science B.V. All rts. reserv.

10885194 EMBASE No: 2000368627
Role of platelet P-selectin and CD40 ligand in the induction of monocytic tissue factor expression
Lindmark E.; Tenno T.; Siegbahn A.
Dr. A. Siegbahn, Department of Medical Sciences, Clinical Chemistry, University Hospital, S-75185 Uppsala Sweden
AUTHOR EMAIL: agneta.siegbahn@klinkem.uas.lul.se
Arteriosclerosis, Thrombosis, and Vascular Biology (ARTERIOSCLER. THROMB. VASC. BIOL.) (United States) 2000, 20/10 (2322-2328)
CODEN: ATVBF ISSN: 1079-5642
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 23

7/3/25 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2003 Elsevier Science B.V. All rts. reserv.

10670322 EMBASE No: 2000153454
Soluble P-selectin in human plasma: Effect of anticoagulant matrix and its levels in patients with cardiovascular disorders
Amin H.M.; Ahmad S.; Walenga J.M.; Hoppensteadt D.A.; Leitz H.; Fareed J.
Dr. J. Fareed, Hemostasis and Thrombosis Res. Lab., Loyola University Medical Center, 2160 S. First Avenue, Maywood, IL 60153 United States
AUTHOR EMAIL: jfareed@luc.edu
Clinical and Applied Thrombosis/Hemostasis (CLIN. APPL. THROMB. HEMOST.) (United States) 2000, 6/2 (71-76)
CODEN: CATHF ISSN: 1076-0296
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 29

7/3/26 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2003 Elsevier Science B.V. All rts. reserv.

10645829 EMBASE No: 2000111200
Direct observations in vivo on the role of endothelial selectins and alphainf 4 integrin in cytokine-induced leukocyte-endothelium interactions in the mouse aorta
Eriksson E.E.; Werr J.; Guo Y.; Thoren P.; Lindborn L.
E.E. Eriksson, Dept. of Physiology and Pharmacology, Karolinska Institutet, S-171 77 Stockholm Sweden
AUTHOR EMAIL: einar.eriksson@fyfa.ki.se
Circulation Research (CIRC. RES.) (United States) 17 MAR 2000, 86/5 (526-533)
CODEN: CIRUA ISSN: 0009-7330
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 31

7/3/27 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2003 Elsevier Science B.V. All rts. reserv.

10582186 EMBASE No: 2000046990
Paradoxical inhibition of fibrinogen binding and potentiation of alpha-granule release by specific types of inhibitors of glycoprotein

IIb-IIIa
Schneider D.J.; Taatjes D.J.; Sobel B.E.
D.J. Schneider, Department of Medicine, University of Vermont, Burlington, Colchester, VT 05446 United States
AUTHOR EMAIL: djschnei@zoo.uvm.edu
Cardiovascular Research (CARDIOVASC. RES.) (Netherlands) 2000, 45/2 (437-446)
CODEN: CVREA ISSN: 0008-6363
PUBLISHER ITEM IDENTIFIER: S0008636399002539
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 23

7/3/28 (Item 8 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2003 Elsevier Science B.V. All rts. reserv.

10572459 EMBASE No: 2000037327
Role of transforming growth factor-beta1 in cardiovascular inflammatory changes induced by chronic inhibition of nitric oxide synthesis
Koyanagi M.; Egashira K.; Kubo-Inoue M.; Usui M.; Kitamoto S.; Tomita H.; Shimokawa H.; Takeshita A.
Dr. K. Egashira, Dept. of Cardiovascular Medicine, Graduate School of Medical Sciences, Kyushu University, 3-1-1, Maidashi, Higashi-ku, Fukuoka 812-8582 Japan
AUTHOR EMAIL: egashira@cardiol.med.kyushu-u.ac.jp
Hypertension (HYPERTENSION) (United States) 2000, 35/1 I (86-90)
CODEN: HPRTD ISSN: 0194-911X
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 29

7/3/29 (Item 9 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2003 Elsevier Science B.V. All rts. reserv.

07842886 EMBASE No: 1999090354
Circulating platelets show increased activation in patients with acute cerebral ischemia
Zeller J.A.; Tschoepe D.; Kessler C.
Dr. J.A. Zeller, Department of Neurology, Christian-Albrechts-University Kiel, Niemannsweg 147, D-24105 Kiel Germany
AUTHOR EMAIL: j.zeller@neurologie.uni-kiel.de
Thrombosis and Haemostasis (THROMB. HAEMOST.) (Germany) 1999, 81/3 (373-377)
CODEN: THHAD ISSN: 0340-6245
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 39

7/3/30 (Item 10 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2003 Elsevier Science B.V. All rts. reserv.

06816856 EMBASE No: 1997099348
Effects of monoclonal **antibody** to **P-selectin** and analogue of sialyl Lewis X on cyclic flow variations in stenosed and endothelium-injured canine coronary arteries
Ueyama T.; Ikeda H.; Haramaki N.; Kuwano K.; Imaizumi T.
Dr. H. Ikeda, Third Dept. of Internal Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume, 830 Japan

Circulation (CIRCULATION) (United States) 1997, 95/6 (1554-1559)
CODEN: CIRCA ISSN: 0009-7322
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 43

7/3/31 (Item 11 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2003 Elsevier Science B.V. All rts. reserv.

06320554 EMBASE No: 1995357505
Peptido-leukotrienes are potent agonists of von Willebrand factor secretion and P-selectin surface expression in human umbilical vein endothelial cells
Datta Y.H.; Romano M.; Jacobson B.C.; Golan D.E.; Serhan C.N.; Ewenstein B.M.
CETRI, 75 Francis St,Boston, MA 02115 United States
Circulation (CIRCULATION) (United States) 1995, 92/11 (3304-3311)
CODEN: CIRCA ISSN: 0009-7322
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

7/3/32 (Item 12 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2003 Elsevier Science B.V. All rts. reserv.

05383475 EMBASE No: 1993151574
Blood monocyte adhesion to vascular endothelial cells. Implication in vascular pathology
Dosquet C.; Wautier J.-L.
Lab de Biologie Vasculaire/, Cellulaire, Hopital Lariboisiere, 2 rue Ambroise Pare,75010 Paris France
Clinical Hemorheology (CLIN. HEMORHEOL.) (United States) 1992, 12/6 (817-829)
CODEN: CLHED ISSN: 0271-5198
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

7/3/33 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12717353 21335306 PMID: 11442315
Hypercholesterolemia alters endotoxin-induced endothelial cell adhesion molecule expression.
Cerwinka W H; Cheema M H; Granger D N
Department of Molecular and Cellular Physiology, Louisiana State University Health Sciences Center, Shreveport 71130-3932, USA.
Shock (Augusta, Ga.) (United States) Jul 2001, 16 (1) p44-50, ISSN 1073-2322 Journal Code: 9421564
Contract/Grant No.: HL26441; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

7/3/34 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10925688 20502863 PMID: 11044430
Angiotensin II induces leukocyte-endothelial cell interactions in vivo

via AT(1) and AT(2) receptor-mediated P-selectin upregulation.
Piqueras L; Kubes P; Alvarez A; O'Connor E; Issekutz A C; Esplugues J V; Sanz M J
Department of Pharmacology, University of Valencia, Spain.
Circulation (UNITED STATES) Oct 24 2000, 102 (17) p2118-23, ISSN 1524-4539 Journal Code: 0147763
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

7/3/35 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10453083 99445382 PMID: 10515876
Circulating activated platelets assist THP-1 monocytoid/endothelial cell interaction under shear stress.
Theilmeier G; Lenaerts T; Remacle C; Collen D; Vermylen J; Hoylaerts M F
Center for Molecular and Vascular Biology, Katholieke Universiteit Leuven, Leuven, Belgium.
Blood (UNITED STATES) Oct 15 1999, 94 (8) p2725-34, ISSN 0006-4971 Journal Code: 7603509
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

7/3/36 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
(c) 2003 American Chemical Society. All rts. reserv.

133280563 CA: 133(20)280563a PATENT
Human antibodies that bind human IL-12 and methods for producing
INVENTOR(AUTHOR): Salfeld, Jochen G.; Roguska, Michael; Paskind, Michael; Banerjee, Subhashis; Tracey, Daniel E.; White, Michael; Kaymakcalan, Zehra; Labkovsky, Boris; Sakorafas, Paul; Friedrich, Stuart; Myles, Angela; Veldman, Geertruida M.; Venturini, Amy; Warne, Nicholas W.; Widom, Angela; Elvin, John G.; Duncan, Alexander R.; Derbyshire, Elaine J.; Carmen, Sara; Smith, Stephen; Holtet, Thor Las; Du, Fou Sarah L.
LOCATION: Germany,
ASSIGNEE: Basf A.-G.; Genetics Institute Inc.; et al.
PATENT: PCT International ; WO 200056772 A1 DATE: 20000928
APPLICATION: WO 2000US7946 (20000324) *US PV126603 (19990325)
PAGES: 377 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C07K-016/24A; C12N-015/13B; C12N-015/63B; C12N-005/10B; C07K-016/00B; A61K-039/395B; G01N-033/577B; C12P-021/08B; A61P-043/00B DESIGNATED COUNTRIES: AE; AG; AL ; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CR; CU; CZ; DE; DK; DM; DZ; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MA; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; TZ; UA; UG; US; UZ; VN; YU; ZA; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM ; KE; LS; MW; SD; SL; SZ; TZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG

7/3/37 (Item 2 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
(c) 2003 American Chemical Society. All rts. reserv.

124135703 CA: 124(11)135703f PATENT
Method using agents inhibiting interaction between P-selectin??? and a

P-selectin ligand for treating and preventing atherosclerosis
INVENTOR(AUTHOR): Wagner, Denisa D.; Johnson, Robert C.
LOCATION: USA
ASSIGNEE: Center for Blood Research, Inc.
PATENT: PCT International ; WO 9533484 A1 DATE: 951214
APPLICATION: WO 95US6940 (950601) *US 253663 (940603) *US 377798 (950124)
PAGES: 35 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: A61K-039/395A; A61K-038/02B; A61K-038/16B; A61K-031/70B DESIGNATED COUNTRIES: CA; JP
DESIGNATED REGIONAL: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE

7/3/38 (Item 3 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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119026686 CA: 119(3)26686d PATENT
Inhibition of vascular narrowing using anti-PADGEM antibodies
INVENTOR(AUTHOR): Palabrica, Theresa M.; Furie, Bruce E.; Furie, Barbara C.
LOCATION: USA
ASSIGNEE: Biogen, Inc.; New England Medical Center Hospitals, Inc.
PATENT: PCT International ; WO 9306863 A1 DATE: 930415
APPLICATION: WO 92US8163 (920930) *US 768834 (910930)
PAGES: 32 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: A61K-039/395A
DESIGNATED COUNTRIES: AT; AU; BB; BG; BR; CA; CH; CS; DE; DK; ES; FI; GB; HU; JP; KP; KR; LK; LU; MG; MN; MW; NL; NO; PL; RO; RU; SD; SE; US
DESIGNATED REGIONAL: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LU; MC; NL; SE; BF; BJ; CF; CG; CI; CM; GA; GN; ML; MR; SN; TD; TG
?

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L5: Entry 42 of 94 File: USPT Nov 2, 1999

DOCUMENT-IDENTIFIER: US 5976532 A
TITLE: Method of antithrombotic therapy using anti-GPIIb/IIIa antibodies or fragments thereof, including c7E3

Detailed Description Text (6):
Examples of suitable antibodies specific for platelets include 7E3 and 10E5. See European Patent Application Nos. 205,207 and 206,532, the teachings of which are incorporated herein. The 7E3 antibody (or antibody reactive with the same or a functionally equivalent epitope) is especially preferred because it is specific for the the complexed form of the GPIIb/IIIa receptor. Other antibodies specific for the GPIIb/IIIa receptor (antigen recognized by 7E3), such as those specific for either the IIb or IIIa components, can also be used. Antibodies specific for other platelet antigens can be employed. For example, antibodies reactive with platelet .alpha. granule membrane protein GMP-140 such as S12 antibody (J. Biol. Chem. 259:9799-9804 (1984)) can be used.

Other Reference Publication (61):
Wagner, C.L. et al., "Molecular Pharmacology of Chimeric 7E3 Monoclonal Fab Fragment Binding to Platelet GPIIb/IIIa Receptors", Atherosclerosis and Thrombosis, 11: 1594a (1991).

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L5: Entry 49 of 94 File: USPT Jul 27, 1999

DOCUMENT-IDENTIFIER: US 5929036 A
TITLE: Ligand or GMP-140 selectin and methods of use thereof

Abstract Text (1):
Fucosylated sialyated lactosaminoglycan structures that bind to GMP-140 have been discovered. The structure is created by expression of .alpha.(1,3) fucosyltransferases capable of modifying acceptors containing .alpha.(2,3) sialic acid-substituted lactosaminoglycans. Le.sup.x, Gal.beta.1,4(Fuc.alpha.1,3) GlcNAc.beta.1-R (where R is a protein or other carbohydrate structure), a common trisaccharide structure on myeloid cells but not on lymphocytes or erythroid cells, forms the core of this sialyated structure. The actual structure may be sialyl Le.sup.x, difucosyl sialyl Le.sup.x, a longer polyfucosylated polyactosaminoglycan, or a related variant. Several of these structures may bind to GMP-140 with various degrees of affinity. The carbohydrate structures, including sialyl Le.sup.x, difucosyl sialyl Le.sup.x, or a longer polyfucosylated polyactosaminoglycan variant, produced synthetically or expressed in genetically engineered cells, are useful as diagnostics and, in combination with a suitable pharmaceutical carrier, for clinical applications in the modulation or inhibition of coagulation processes or inflammatory processes. Antibodies to these structures can also be used as diagnostics and as pharmaceuticals for modulation of the coagulation or inflammatory processes.

Brief Summary Text (13):
In November 1990, Larsen, et al, in Cell 63: 467-474 (1990), claimed that Le.sup.x is, or is a major "component" of the ligand, based on inhibition of neutrophil or HL60 cell binding to activated platelets (which express GMP-140) or to COS cells transfected with GMP-140 cDNA. The inhibition was either with high concentrations of monoclonal antibodies to Le.sup.x or with concentrations of LNFIII up to 300 .mu.M. LNFIII is Gal.beta.1,4(Fuc.alpha.1,3)GlcNAc.beta.1,3Gal.beta.1,4Glc; thus it includes the Le.sup.x trisaccharide.

Drawing Description Text (3):
FIG. 2 is a graph of the effect of monoclonal antibodies on the binding of NeoLewis CHO cells to immobilized GMP-140, % binding of control for control (dark bar), in the presence of G1 antibody (///), in the presence of S12 antibody (++++), and in the presence of EDTA (/ / /).

Drawing Description Text (4):
FIG. 3 is a graph of neutrophils bound (.times.10.sup.-4) by monolayers of COS cells transfected with no cDNA (Mock) or with cDNAs encoding either ELAM-1 or GMP-140 in the presence or absence of fluid-phase inhibitors of binding. The inhibitors were: for ELAM-1-transfected cells--none, GMP-140, and H18/7 (a monoclonal antibody that recognizes ELAM-1 but not GMP-140 binding and blocks neutrophil adhesion to ELAM-1); and for GMP-140-transfected cells--none, GMP-140 (GMP), and G1 (a monoclonal antibody that recognizes GMP-140 but not ELAM-1 and blocks neutrophil adhesion to GMP-140).

Drawing Description Text (5):
FIG. 4 is a graph of neutrophils (polymorphonuclear leukocytes or PMN) and HT-29 cells (which express sialyl Le.sup.x) bound (.times.10.sup.-4) by transfected COS cells: control, by ELAM-1 alone or in the presence of H18/7 antibody which blocks binding by ELAM-1 but not GMP-140, and by GMP-140 alone or in the presence of G1 antibody which blocks binding by GMP-140 but not ELAM-1.

Detailed Description Text (6):
Other data with transfected cell lines described in detail in example 2 indicate that a sialyated fucosylated lactosamine with .alpha.2,3-linked sialic acid is sufficient for recognition. It is believed the carbohydrate is not Le.sup.x alone since an antibody to Le.sup.x does not block binding of [.sup.125 I]GMP-140 to neutrophils. Studies comparing binding of GMP-140 with two different multivalent neoglycoconjugates, in which either sialyl Le.sup.x or Le.sup.x was coupled to bovine serum albumin at a molar ratio of about 10:1, in high concentrations (6.5 .mu.M of conjugate, 65 .mu.M of oligosaccharide) also failed to inhibit binding, suggesting that neither Le.sup.x nor sialyl Le.sup.x per se is the ligand or that the affinity of these oligosaccharides for GMP-140 is too low to measure by this assay.

Detailed Description Text (12):
As described in U.S. Ser. No. 07/554,199, the ability of the lectin 19-34 peptide to prevent binding to GMP-140 of all three monoclonal antibodies that block interactions of GMP-140 with leukocytes provides additional proof of the importance of the lectin domain in leukocyte recognition. It is postulated from this data that the conformation of the lectin domain is modulated by interactions with the EGF domain; these interactions in turn are modulated by divalent cations, which may bind to both the lectin and EGF domains. The result is a three-dimensional conformation of the lectin domain that confers affinity and specificity of binding to its receptor(s) on neutrophils and monocytes.

Detailed Description Text (28):
To test the ability of these cells to interact with GMP-140, a slight modification of the adhesion assay used for neutrophils and HL60 cells (J.-G. Geng et al, Nature 343: 757-760, 1990) was used with purified GMP-140 and monoclonal antibodies to GMP-140. GMP-140 was immobilized on plastic wells in increasing concentrations and the wells were then blocked with albumin-containing buffer. CHO or HL-60 cells, metabolically labeled with [.sup.35 S]methionine, were added to the wells in the presence or absence of Ca.sup.2+, and adhesion was measured by solubilizing the bound cells and quantitating the radioactivity.

Detailed Description Text (30):
The HL-60 cells bound specifically to GMP-140-coated wells in a Ca.sup.2+ -dependent manner, as previously noted (Geng, et al, Nature 343: 757-760 (1990)). The wild type CHO cells, the Lec 8 CHO cells, and the NeoLewis related CHO cells did not bind. However, like the HL-60 cells, the NeoLewis CHO cells bound avidly to immobilized GMP-140 in a Ca.sup.2+ -dependent manner. The adhesion was specific, because it was prevented by G1, a blocking monoclonal antibody to GMP-140, but not by S12, a nonblocking antibody, as shown in FIG. 2. The adhesion was critically dependent on sialic acid, because treatment of the NeoLewis CHO cells with neuraminidase from Vibrio cholera abolished binding. Pretreatment of the NeoLewis CHO cells with trypsin reduced binding by 60%, suggesting that at least a substantial fraction of the oligosaccharide ligands for GMP-140 on the cells are carried by a protein(s).

Detailed Description Text (36):
First, neutrophils adhere specifically to COS cells transfected with cDNAs encoding either GMP-140 or ELAM-1. As previously noted by Geng, et al, Nature (1990), adhesion to GMP-140-transfected cells was blocked by G1, a monoclonal antibody to GMP-140, and adhesion to ELAM-1-transfected cells was blocked by H18/7, a monoclonal antibody to ELAM-1. However, while fluid-phase GMP-140 blocked neutrophil adhesion to GMP-140-transfected cells, it had no effect on adhesion to ELAM-1-transfected cells (FIG. 3).

Detailed Description Text (48):
The results clearly demonstrate that neutrophils bind to COS cells transfected with cDNAs encoding either ELAM-1 or GMP-140 and that the binding is inhibited by appropriate monoclonal antibodies: the anti-ELAM-1 antibody (H18/7) blocks binding of neutrophils to ELAM-1-transfected cells and the anti-GMP-140 antibody (G1) blocks binding of neutrophils to GMP-140-transfected COS cells. However, fluid-phase GMP-140, while completely blocking neutrophil adhesion to GMP-140-transfected COS cells, has no effect on neutrophil adhesion to ELAM-1-transfected COS cells.

Detailed Description Text (54):
In the case of neutrophils, it has been established that a major glycoprotein recognized by GMP-140,has an apparent Mr of approximately 120,000 as analyzed by SDS-PAGE under reducing conditions. A plasma membrane fraction of human neutrophils was prepared and the material analyzed by "ligand blotting." The material was fractionated by SDS-PAGE, transferred to Immobilon membranes, and probed with [.sup.125]GMP-140. Consistent binding of labeled GMP-140 to a 120-kD band under reducing conditions was observed. The binding is specific, because it is Ca.sup.2+ -dependent, blocked by antibody G1 but not S12, and eliminated by prior treatment of the membrane with neuraminidase. This protein is bound quantitatively on a wheat germ agglutinin affinity column, indicating that it contains extensively sialylated oligosaccharides.

Detailed Description Text (60):
Antibodies or other probes to the carbohydrate can be used for the detection of human disorders in which GMP-140 ligands might be defective. Such disorders would most likely be seen in patients with increased susceptibility to infections in which leukocytes might not be able to bind to activated platelets or endothelium. Cells to be tested, usually leukocytes, are collected by standard medically approved techniques and screened. Detection systems include. ELISA procedures, binding of radiolabeled antibody to immobilized activated cells, flow cytometry, or other methods known to those skilled in the arts. Leukocytes deficient in ligands for GMP-140 would demonstrate defective binding of antibodies to the ligand or of GMP-140 itself.

Detailed Description Text (65):
An inflammatory response may cause damage to the host if unchecked, because leukocytes release many toxic molecules that can damage normal tissues. These molecules include proteolytic enzymes and free radicals. Examples of pathological situations in which leukocytes can cause tissue damage include injury from ischemia and reperfusion, bacterial sepsis and disseminated intravascular coagulation, adult respiratory distress syndrome, tumor metastasis, rheumatoid arthritis and atherosclerosis.

Detailed Description Text (72):
Platelet-leukocyte interactions are believed to be important in atherosclerosis. Platelets might have a role in recruitment of monocytes into atherosclerotic plaques; the accumulation of monocytes is known to be one of the earliest detectable events during atherogenesis. Rupture of a fully developed plaque may not only lead to platelet deposition and activation and the promotion of thrombus formation, but also the early recruitment of neutrophils to an area of ischemia.

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L5: Entry 52 of 94 File: USPT Jun 29, 1999

DOCUMENT-IDENTIFIER: US 5916876 A
TITLE: Peptide inhibitors of leukocyte adhesion

Detailed Description Text (60):
P-selectin is isolated from human platelet lysates by immunoaffinity chromatography on antibody S12-Sepharose.TM. and ion-exchange chromatography on a Mono-Q.TM. column (FLPC, Pharmacia Fine Chemicals), as follows.

Detailed Description Text (63):
The soluble fraction (0.5 M NaCl wash) and the membrane extract (also adjusted to 0.5 M NaCl) are absorbed with separate pools of the monoclonal antibody S12 (directed to P-selectin) previously coupled to Affigel (Biorad) at 5 mg/mL for 2 hours at 4.degree. C. After letting the resins settle, the supernatants are removed. The S12 Affigel containing bound GMP-140 is then loaded into a column and washed overnight at 4.degree. C. with 400 mL of 0.5 M NaCl, 20 mM Tris pH 7.5, 0.01% Lubrol PX.

Detailed Description Text (69):
An inflammatory response may cause damage to the host if unchecked, because leukocytes release many toxic molecules that can damage normal tissues. These molecules include proteolytic enzymes and free radicals. Examples of pathological situations in which leukocytes can cause tissue damage include injury from ischemia and reperfusion, bacterial sepsis and disseminated intravascular coagulation, adult respiratory distress syndrome, tumor metastasis, rheumatoid arthritis and atherosclerosis.

Detailed Description Text (75):
Tumor cells from many malignancies (including carcinomas, lymphomas, and sarcomas) can metastasize to distant sites through the vasculature. The mechanisms for adhesion of tumor cells to endothelium and their subsequent migration are not well understood, but may be similar to those of leukocytes in at least some cases. The association of platelets with metastasizing tumor cells has been well described, suggesting a role for platelets in the spread of some cancers. Recently, it was reported that P-selectin binds to tumor cells in a variety of human carcinoma tissue sections (colon, lung, and breast), and that P-selectin binds to the cell surface of a number of cell lines derived from various carcinomas, but not from melanomas. Aruggo, A., et al., Proc. Natl. Acad. Sci. USA, 89, 2292-2296 (1992). Aruggo et al. also reference earlier work suggesting that E-selectin might be involved in tumor metastasis by mediating the adhesion of a colon carcinoma cell line (HT-20) to activated endothelial cells in vitro. Platelet-leukocyte interactions are believed to be important in atherosclerosis. Platelets might have a role in recruitment of monocytes into atherosclerotic plaques; the accumulation of monocytes is known to be one of the earliest detectable events during atherogenesis. Rupture of a fully developed plaque may not only lead to platelet deposition and activation and the promotion of thrombus formation, but also the early recruitment of neutrophils to an area of ischemia.

Detailed Description Text (79):
The peptides can also be used for the detection of human disorders in which the ligands for the selectins might be defective. Such disorders would most likely be seen in patients with increased susceptibility to infections in which leukocytes might not be able to bind to activated platelets or endothelium. Cells to be tested, usually leukocytes, are collected by standard medically approved techniques and

screened. Detection systems include ELISA procedures, binding of radiolabeled antibody to immobilized activated cells, flow cytometry, or other methods known to those skilled in the art. Inhibition of binding in the presence and absence of the lectin domain peptides can be used to detect defects or alterations in selectin binding. For selectins, such disorders would most likely be seen in patients with increased susceptibility to infections in which leukocytes would have defective binding to platelets and endothelium because of deficient leukocyte ligands for P-selectin.

Detailed Description Text (80):
The peptide is labeled radioactively, with a fluorescent tag, enzymatically, or with electron dense material such as gold for electron microscopy. The cells to be examined, usually leukocytes, are incubated with the labeled peptides and binding assessed by methods described above with antibodies to P-selectin, or by other methods known to those skilled in the art. If ligands for P-selectin are also found in the plasma, they can also be measured with standard ELISA or radioimmunoassay procedures, using labeled P-selectin-derived peptide instead of antibody as the detecting reagent.

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L5: Entry 66 of 94 File: USPT Sep 15, 1998

DOCUMENT-IDENTIFIER: US 5807745 A
TITLE: Method of inhibiting PADGEM-mediated or ELAM-1-mediated leukocyte adhesion using an inhibitor comprising a Le.sup.x core component

Brief Summary Text (5):
Stimulated platelets bind to neutrophils and monocytes through specific recognition sites present on both cell types. This interaction is calcium dependent (Larsen, E. et al., Cell 59: 305-312 (1989); Hamburger, S. A. and McEver, R. P., Blood, 75: 550-554 (1990)). Studies demonstrating the inhibition of this interaction by anti-PADGEM antibodies or by purified PADGEM, indicate that PADGEM expressed on the platelet surface mediates this interaction (Larsen, E. et al., Cell, 59: 305-312 (1989)). Although the lectin-like domains of PADGEM and the other selectins show sequence similarity to calcium-dependent mammalian lectins (Drickamer, K., J. Biol. Chem., 263: 9557-9560 (1988)), the natural ligands for the selectins have not been identified.

Brief Summary Text (8):
The present invention relates to a method of inhibiting (reducing or preventing) the interaction or adhesion of platelets and/or endothelial cells with white blood cells (leukocytes) by contacting the platelets and/or endothelial cells with an inhibitor comprising a Lewis x (Le.sup.x) core under conditions whereby adhesion is inhibited. By the method of the present invention, it is possible to inhibit the interaction of a PADGEM-bearing cell, such as a platelet or endothelial cell, with a cell bearing a PADGEM ligand (e.g., neutrophils and monocytes) by contacting the cell with an inhibitor comprising a Le.sup.x core component. As shown herein, antibodies directed against the CD15 cell surface antigen inhibit the interaction of PADGEM-bearing cells (e.g. platelets and COS cells bearing PADGEM) with leukocytes (e.g. neutrophils, monocytes). Furthermore, as is shown herein, Lacto-N-fucopentaose (LNF-III), a complex carbohydrate which comprises a Le.sup.x core component and is recognized by CD15 antibodies, inhibits the binding of stimulated platelets to neutrophils. Thus, the inhibitor can comprise a CD15 immunoreactive carbohydrate, such as Le.sup.x or all or portion of LNF-III. It will be appreciated that inhibitors useful in the present method comprise .alpha.(1-3)fucosylated lactosamine and polylactosamine derivatives.

Drawing Description Text (6):
FIG. 5 illustrates the results of a FACS analysis of the interaction of U937 cells with phospholipid vesicles containing purified PADGEM. A histogram of log red fluorescence is given on the X axis and cell number is given on the Y axis. U937 binding to phospholipid vesicles without PADGEM (dotted line), to phospholipid vesicle containing PADGEM (dashed and dotted line), and to phospholipid vesicles containing PADGEM in the presence of anti-CD15 antibody (solid line) is shown.

Detailed Description Text (4):
To identify the natural PADGEM ligand on neutrophils and monocytes, a series of monoclonal antibodies prepared against a variety of leukocytes and derivative cell lines was surveyed to identify those that bind to structures on leukocytes, but do not bind to platelets, and those that also inhibit the interaction of activated platelets with leukocytes. Of the antibodies surveyed, only those directed against CD15 met these criteria. As shown in Example 3, antibodies directed against the CD15 cell surface antigen inhibit the interaction of PADGEM-bearing cells (e.g. platelets and COS cells bearing PADGEM) with leukocytes (e.g. neutrophils, monocytes). The observation that antibodies to CD15 blocked the interaction of activated platelets

with neutrophils, monocytes, HL60 cells, and U937 cells suggested that CD15 on the white cell surface may be directly involved with or located in close proximity to the PADGEM ligand. In fact, several lines of evidence indicate that the PADGEM ligand actually shares structural features with CD15 positive structures.

Detailed Description Text (6):
Thus, the observation that three different anti-CD15 monoclonal antibodies inhibit the binding of activated platelets to monocytes and neutrophils, and that the distribution of CD15 on different vascular cells is parallel to the distribution of the PADGEM ligand, suggests that the PADGEM ligand and CD15 antigen are related. The demonstration in Example 3 that CD15 antibodies also inhibit the interaction of monocyte-like cells (U937) with COS cells transfected with PADGEM or with phospholipid vesicles containing purified PADGEM emphasizes the specificity of the anti-CD15 antibody inhibition for PADGEM mediated adhesion.

Detailed Description Text (7):
As shown in Example 4, purified forms of LNF III inhibit the interaction of activated platelets with neutrophils and monocytes. COS cells expressing PADGEM were shown to bind to HL60 and U937 cells, whereas COS cells not expressing PADGEM did not; this interaction was inhibited by LNF III or anti-CD15 antibodies (Example 4). Thus, inhibition by LNF III involves a process that is mediated by PADGEM on activated platelets.

Detailed Description Text (12):
In one embodiment, the interaction of a PADGEM-bearing cell (e.g., a platelet, an endothelial cell) with a cell bearing a PADGEM ligand, such as a neutrophil or a monocyte, is inhibited by contacting the PADGEM-bearing cell with an inhibitor comprising a Le.sup.x core component. For example, Lacto-N-fucopentaose (LNF III), a complex carbohydrate which comprises a Le.sup.x core component and is recognized by CD15 antibodies, inhibits the binding of stimulated platelets to neutrophils (FIG. 6). As shown herein, LNF III also inhibits the interaction of HL60 cells (monocyte-like cells) with COS cells that were transfected with PADGEM (FIG. 7). COS cells are fibroblast-like SV40-transformed African Green Monkey kidney cells. Therefore, LNF III inhibits the adhesion involving cells which naturally express PADGEM (e.g. nuetrophils and monocytes), as well as adhesion involving cells artificially induced to express PADGEM (e.g. PADGEM-transfected cells). Thus, the inhibitor can comprise a CD15 immunoreactive carbohydrate, such as LNF III.

Detailed Description Text (25):
In a model of atherosclerosis, injured endothelial cells in a vessel wall express PADGEM on their surface. Monocytes bearing a PADGEM ligand are recruited to the site by virtue of PADGEM--PADGEM ligand interaction, and adhere to the endothelial cells. The monocytes become pathological foam cells by ingestion of lipids, platelet fragments, and other molecules. However, the atherosclerotic process can be inhibited by contacting the PADGEM-bearing endothelial cells with an inhibitor comprising a Le.sup.x core, which inhibits PADGEM-mediated adhesion.

Detailed Description Text (27):
For use in treating a condition in an individual in which a surface molecule capable of interacting with a Le.sup.x core plays a role in pathological process (e.g., atherosclerosis, thrombolysis, inflammation, or metastasis), inhibitors of the present invention are administered by an appropriate route (e.g., intravenously, parenterally or topically). Treatment is under appropriate conditions and in amounts sufficient to reduce or prevent adhesion and thereby, reduce or prevent the disease process. For example, an inhibitor can be combined with a suitable carrier, incorporated into a liposome, or polymer release system for administration.

Detailed Description Text (32):
Antibody 80H5 was purchased from AMAC, Inc. Other antibodies were the generous gifts of Drs. Dennis Hickstein and John Harlan (7C3), Dr. Paul Guyre (PM81, 168, AML-2-23), and Dr. Douglas Faller (TS1/18, OKM15, TS2/9, W6/32, LB3.1, GAP8.3, 4F2, and 63D3). Polyclonal anti-PADGEM antibodies were raised in rabbits and isolated by affinity chromatography on PADGEM-Sepharose, as previously described (Berman et al., J. Clin. Invest., 78: 130-137 (1986)). The monoclonal anti-PADGEM antibody AC1.2 has been previously described (Larsen et al., Cell 59: 305-312 (1989)). LNF I, LNF II,

and LNF III, purchased from Calbiochem, were greater than 95% pure by HPLC, as assayed by the supplier.

Detailed Description Text (42):
The presence of PADGEM expression in the transfected COS/PADGEM cells was demonstrated by immunofluorescent staining using the monoclonal antibody AC1.2. Cells were incubated with the anti-PADGEM monoclonal antibody AC1.2 (Bonfanti et al., Blood 73: 1109-1112 (1989)) and stained with rhodamine conjugated to goat anti-mouse antibody. The immunoflourescence data indicated that, in these experiments, 10%-20% of the COS cells expressed PADGEM. Furthermore, HL60 cells, from a human cell line that exhibits monocyte-like characteristics, and which bind to platelets in a PADGEM-dependent manner (Larsen, E. et al., Cell 59: 305-312 (1989)) were found to bind to COS cells expressing PADGEM (COS/PADGEM transfectants). In contrast, the HL60 cells did not bind to COS cells that were subjected to mock transfection. These results indicated that the COS-PADGEM transfectants retain adhesive properties of PADGEM.

Detailed Description Text (53):
PADGEM was incorporated into phospholipid vesicles as previously described (Larsen et al., Cell 59: 305-312 (1989)) with some modifications. Briefly, 5 mg of egg phosphatidylcholine (Avanti Polar Lipids) and 0.025 mg of Di IC.sub.16 (3) (1,1'-dihexadecyl-3,3,3',3'-tetramethyl-lindocarbocyanine perchlorate) (Molecular Probes) in chloroform were mixed, and the chloroform was removed by evaporation at 37.degree. C. under nitrogen. The dried lipids were resuspended in methylene chloride, and the solvent was removed by evaporation. Purified PADGEM (1 ml; 65 .mu.g/ml; Larsen et al., Cell 59: 305-312 (1989)) in Tris-buffered saline containing 50 mM octyl-.beta.-D-glucopyranoside (Calbiochem) or Tris-buffered saline along containing 50 mM octyl-.beta.-D-glucopyranoside (1 ml) was added to the dried phospholipids, and the lipids were resuspended. The preparations were dialyzed under nitrogen against Tris-buffered saline-0.02% NaN.sub.3 for 24 hours. Vesicles were separated from free protein by gel filtration on a Sepharose 4B column. Phospholipid vesicles (50 .mu.l) with or without PADGEM were incubated with 2.times.10.sup.5 U937 cells in RPMI 1640, 1% fetal calf serum, 2% bovine serum albumin for 30 minutes at 23.degree. C. For experiments with 80H5 antibody, U937 cells were incubated with the antibody (5 .mu.g/ml) for 1 hour; phospholipid vesicles were added, and the incubation was continued for an additional 30 minutes. Prior to analysis on a FACScan (Becton Dickinson), each sample was diluted 10 fold with RPMI 1640, 1% fetal calf serum, 2% bovine serum albumin. U937 cells were identified by their forward and side light scatter profiles, and binding of PADGEM in phospholipid vesicles was quantitated by measuring red fluorescence. Data were collected for 3000 cells.

Detailed Description Text (57):
Thrombin-activated platelets bind to human neutrophils, monocytes, HL60 cells and U937 cells in an interaction that is mediated by PADGEM on the surface of the platelet (Larsen et al., Cell 59: 305-312 (1989). This interaction is inhibited by anti-PADGEM antibodies and purified PADGEM. Unstimulated platelets, which do not express PADGEM on the platelet surface, do not interact with these leukocytes.

Detailed Description Text (58):
To identify the PADGEM recognition site on leukocytes that mediates the binding of activated platelets, monoclonal antibodies directed at various antigens on the surface of monocytes and neutrophils were tested for their ability to inhibit the interaction of these cells with activated platelets, using the phase-contrast cell adhesion assay described in Example 2 (FIG. 1 and FIG. 2). The antibodies were raised against various leukocytes and myeloid cell lines and are directed at leukocyte antigens. The antibodies which were tested and their corresponding antigens are as follows: TS1/18, LFA-1 (.beta.); OKM15, CR3; TS2/9, LFA-3; W6/32, HLA class I; LB3.1, HLA class II; GAP8.3, T200; 4F2, 4F2; 63D3, 63D3; 168, 168; AML-2-23, 2-23; PM81, CD15; 7C3, CD15; 80H5, CD15. These immunochemical reagents included antibodies of the IgG and IgM isotype. The effect of buffer alone (HEPES) on the adherence of activated platelets and neutrophils served as a negative control, while the effect of anti-PADGEM antibodies on cell adherence served as a positive control for inhibition. The percentage of cells displaying two or more adherent platelets was determined as described in Example 2.

Detailed Description Text (59):
With the exception of antibodies which recognize CD15 (PM81, 7C3, and 80H5), none of the other antibodies that were tested demonstrated inhibitory properties. The anti-CD15 monoclonal antibodies, obtained from three separate and independent hybridoma cell lines and of the IgM isotype, each displayed significant inhibition of the interaction between neutrophils and activated platelets (FIG. 1). These results suggest that the anti-CD15 antibodies are targeted against a structure on the leukocyte surface which participates in the PADGEM-mediated binding of leukocytes to activated platelets.

Detailed Description Text (60):
The effect of 80H5 antibodies against CD15 on the interaction of activated platelets with neutrophils, HL60 cells, U937 cells, or monocytes is illustrated in FIG. 2. In the absence of anti-CD15 antibodies (black bars), activated platelets adhered to neutrophils (PMN). However, this binding was inhibited with anti-CD15 antibodies. Similarly, the 80H5 antibody blocked the interaction of activated platelets with monocytes (Mono), U937 cells, and HL60 cells. These leukocytes are known to be CD15 positive, and anti-CD15 antibody was observed to inhibit cell adhesion with thrombin stimulated platelets in each case. In contrast, we confirmed that platelets, which carry PADGEM, but which apparently lack the PADGEM ligand, are CD15 negative. Thus, the distribution of CD15 positivity parallels the expression of PADGEM recognition sites on specific leukocytes (Larsen et al., Cell 59: 305-312 (1989)). Just as anti-PADGEM antibodies directed against PADGEM on platelets can inhibit platelet-leukocyte interaction, anti-CD15 antibodies directed against CD15 on leukocytes inhibit platelet-leukocyte interaction.

Detailed Description Text (61):
Inhibition of PADGEM-Leukocyte Binding with CD15 Antibodies

Detailed Description Text (62):
The inhibition of activated platelet adherence to neutrophils by anti-CD15 antibody was dependent upon the concentration of antibody. Using the anti-CD15 antibody 7C3 (Nauseef et al., Blood 62: 636-644 (1983)) in the phase-contrast adhesion assay (Example 2), half-maximal inhibition was observed at about 30 .mu.g/ml (FIG. 3). Although complete inhibition was not observed, inhibition to the extent of 60%-80% was observed in multiple, independent experiments. Similar results were obtained with other anti-CD15 antibodies, including PM81 and 80H5, or with different cells, including monocytes, HL60 cells, and U937 cells (data not shown). It has been previously demonstrated that the binding of leukocytes (including neutrophils, monocytes, HL60 cells, and U397 cells) to activated platelets is mediated by PADGEM (Larsen, E. et al., Cell 59: 305-312 (1989)). The results shown here suggest that antibodies to CD15, which disrupt cell--cell interactions which are mediated by PADGEM, are directed toward the PADGEM ligand.

Detailed Description Text (63):
To confirm that the inhibitory activity of the anti-CD15 antibodies involves the PADGEM ligand specifically, the effect of anti-CD15 antibodies on the binding of COS/PADGEM cells to .sup.111 In-labeled U937 cells was studied. COS/PADGEM cells were constructed as described in Example 1. The COS cell-PADGEM adhesion assay is described in Example 2. As shown in FIG. 4, anti-CD15 antibody 80H5 inhibited COS/PADGEM binding to U937 cells, indicating that the anti-CD15 antibodies specifically interfere with PADGEM-mediated interactions. These results further emphasize that the anti-CD15 antibodies are directed against the PADGEM ligand, and not a ligand of other proteins that have been implicated in platelet-leukocyte interaction (Silverstein and Nachman, J. Clin. Invest., 79: 867-874 (1987)).

Detailed Description Text (64):
To demonstrate further that the anti-CD15 antibody inhibition of leukocyte-platelet interaction was mediated via PADGEM, the effect of antibodies against CD15 on the binding of PADGEM-containing phospholipid vesicles to U937 cells was determined. Purified PADGEM was incorporated into fluorescently labelled phospholipid vesicles and adhesion of vesicles to U937 cells was monitored on a fluorescence-activated flow cytometer as described in Example 2. As shown in FIG. 5, anti-CD15 antibodies inhibited the interaction of U937 cells with phospholipid vesicles containing PADGEM. Phospholipid vesicles lacking PADGEM did not interact with U937 cells,

confirming previous results (Larsen et al., Cell 59:305-312 (1989)). These results indicate that PADGEM is the complementary structure that is recognized by the target of the anti-CD15 antibody.

Detailed Description Text (67):
CD15 antigen has been identified as a complex carbohydrate; CD15 antibodies react with lacto-N-fucopentaose III (LNF III). This carbohydrate has the structure GAl.beta.1-4(Fuc.alpha.1-3)GlcNAc.beta.1-3Gal.beta.1-4Glc. If the anti-CD15 antibody inhibits the interaction of stimulated platelets and leukocytes by binding the PAGDGEM recognition site of leukocytes, thus precluding the binding of PADGEM on platelets, purified CD15 antigen (e.g., LNF III) should also inhibit platelet-leukocyte interaction, since it would saturate the binding sites on PADGEM.

Detailed Description Text (73):
The data demonstrate that LNF III specifically interferes with PADGEM-mediated cell--cell interactions. The inhibition of PADGEM-mediated cell--cell interactions by anti-CD15 monoclonal antibodies and CD15 antigen (e.g., LNF III), suggests that the PADGEM ligand on leukocytes shares structural features with CD15 positive cell surface structures (CD15 antigens), such as LNF III or Le.sup.x, or a portion thereof.

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L5: Entry 71 of 94 File: USPT May 26, 1998

DOCUMENT-IDENTIFIER: US 5756095 A
TITLE: Antibodies with specificity for a common epitope on E-selectin and L-selectin

Brief Summary Text (17):
Even though many anti-selectin mAbs have been developed, none have been shown to have the ability of recognizing determinants on two distinct selectins. CL2, which recognizes human E-selectin, reacts with dog L-selectin, but not both in the same animal (Abbassi et al., 1991 J. Immuno. 147:2107-2115). Spertini et al. (1991 J. Immunol. 147:942) provide the functional characterization and molecular localization of at least 11 different epitopes on L-selectin, but again none of these are expressed on two different selectins. TQ-1 and Leu-8, which recognize L-selectin, also show a much more restricted pattern of staining and do not stain other selectins. None of the published anti-E-selectin or P-selectin mabs have been shown to react with other selectins. It is intriguing that even though there is a significant level of identity at the amino acid level between the different selectins and a large number of anti-selectin mAbs have been generated, prior to this invention, no antibody has been reported to recognize an epitope shared by two different selectins.

Brief Summary Text (19):
While the inflammatory response of leukocytes is vital to the eradication of invading microorganisms, a substantial and convincing body of evidence indicates that inflammatory phagocytes also cause damage to various organs and tissues when these cells are activated in vivo by soluble inflammatory factors that are generated by inciting pathological events (Harlan, 1985 Blood 65:513-525). The adhesion and spreading of activated neutrophils and mononuclear phagocytes to vascular endothelial cells with the subsequent release of toxic oxidative metabolites and proteases has been implicated in the organ damage observed in diseases, such as, adult respiration distress syndrome (ARDS; shock lung syndrome), glomerulonephritis, acute and chronic allograft rejection; inflammatory skin diseases; rheumatoid arthritis; asthma, atherosclerosis, systemic lupus erythematosus, connective tissue diseases; vasculitis; and ischemia-reperfusion syndromes (ie. limb replantation, myocardial infarction, crush injury, shock, stroke, and organ transplantation). (Reviewed in Harlan, ibid.)

Detailed Description Text (7):
The invention further provides methods for employing such compounds in the diagnosis, prevention and treatment of diseases, such as but not limited to those associated with the inflammatory and immune response, ARDS, glomerulonephritis, acute and chronic allograft rejection, inflammatory skin diseases, rheumatoid arthritis, asthma, atherosclerosis, systemic lupus erythematosus, connective tissue diseases, vasculitis, ischemia-reperfusion injury and cancer. The invention further provides a new research tool for the study of leukocyte-endothelium interactions and the role of adhesion molecules in disease mechanisms.

Detailed Description Text (82):
EL-246 was initially screened on human E-selectin cDNA transfected mouse L1-2 cells by flow cytometry and SDS PAGE/Western blot. As shown in FIG. 1, E-selectin transfected, but not the mock transfected L1-2 cells, stained brightly with EL-246 in flow cytometric analysis indicating a specificity of the antibody for E-selectin. The arrows point to histograms which represent (1) EL-246 staining of L1-2ELAM (2) L1-2 transfectant negative controls, and (3) background staining (second stage control) of the L1-2ELAM transfectants. The molecular weight of the antigen

expressed by the transfectants recognized by EL-246 was approximately 110kD under nonreducing SDS PAGE/Western blot (FIG. 2) which is the appropriate molecular weight for E-selectin. L11-2ELAM NP40 lysate was run on a nonreducing 8% SDS/PAGE and transferred to nitrocellulose. The blots were probed with EL-81 (anti-E-selectin, lane 3), EL-246 (lane 2), and negative control antibody (lane 1). The distance of migration of the molecular weight markers were as indicated. EL-246 also recognized E-selectin cDNA transfected L-cells, but did not recognize P-selectin cDNA transfected cells as shown by flow cytometry and Western blots. As an additional means of showing the reactivity of EL-246 with E-selectin, sections of inflamed tonsil tissue were stained for immunohistological analysis. As shown in FIG. 3, EL-246 stained venules (E-selectin) in inflamed human tonsil. Frozen sections of human tonsil were prepared as described in Example 1 and stained by immunoperoxidase with EL-246 (Magnification, 400.times.). Therefore, using accepted biochemical and molecular criteria EL-246 clearly recognized human E-selectin.

Detailed Description Text (177):
EL-246 was tested to determine whether it could inhibit the ability of activated endothelial cells to support neutrophil rolling. HUVECs were grown on the internal surface of sterile glass capillary tubes and induced to express E-selectin (confirmed by EL-246 staining), as described. The tubes were set up in a system which measures leukocyte interactions with ligands under conditions of shear. The in vitro loop assay was used to analyze the effect of EL-246 on the capacity of neutrophils to roll on activated endothelial cells as described. A rolling interaction was established and then EL-246 was injected into the system. The number of rolling neutrophils within the microscopic field of observation was quantified over time by analysis of individual frames from the videotape recording of the interaction. Under controlled shear conditions, activated HUVECs were quite effective at supporting human and mouse neutrophil rolling (data not shown). To test the effect of EL-246, a rolling interaction between isolated human neutrophils was established and then EL-246 (50 ug/ml final concentration) was injected into the closed loop system, and the effect on neutrophil rolling recorded by videomicroscopy for 10 min. The number of neutrophils rolling on the endothelial cells was determined before and after the injection of EL-246 by analyzing individual frames of the videotape. FIG. 11 A shows a plot of the number of cells rolling on the activated endothelial cells versus time. Within 90 seconds after the injection of EL-246, greater then 75% of the rolling interaction was blocked, and by 4 min the blocking was 100%. In tubes injected with medium alone, no inhibitory effect on the neutrophil rolling was detected. Furthermore antibodies to CD44 and P-selectin had no inhibitory effect in this assay (data not shown).

CLAIMS:

5. The monoclonal antibody or antigen binding fragment according to claim 1, wherein the antibody or antigen binding fragment does not bind to P-selectin.

26. The method according to claim 20 in which said monoclonal antibody binds to L-selectin and E-selectin expressing cells and does not bind to P-selectin.

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L5: Entry 94 of 94 File: USPT Jun 25, 1991

DOCUMENT-IDENTIFIER: US 5026537 A
TITLE: Methods for imaging atherosclerotic plaque

Brief Summary Text (4):
The clinical effects of atherosclerotic plaque are due to its space occupying characteristics which lead to stenosis (narrowing) or its thrombogenic (clot-causing) characteristics which appear related to rupture of the fibrous cap and the resulting ulceration of the plaque surface. As a result, a thrombus will form at the site of the plaque. This, in turn, will almost invariably lead to acute myocardial infarction if present in coronary arteries. See Friedman et al., Am. J. Pathol., 48:19-25 (1966); Schwartz, C.J. Atherosclerosis, 15:1-4 (1972).

Brief Summary Text (6):
The important consequence of these effects is reduction of blood flow to the affected organ (heart, brain, etc.). Atherosclerosis is the underlying cause of 75% of the one million deaths from cardiovascular disease in the United States each year. Atherosclerosis accounts for a large proportion of heart attacks, many strokes, most aneurisms of the lower abdominal aorta, and many cases of peripheral vascular disease. Myocardial infarcts have been imaged with antibodies that localize at the infarct site. See, e.g., Haber et al., U.S. Pat. No. 4,036,945. A need exists for imaging methods of high reliability and high resolution that can be used for diagnosing and monitoring atherosclerotic lesions. This is especially true for those lesions that have ulcerated or fissured, resulting in formation of blood clots.

Brief Summary Text (8):
This invention pertains to an method of imaging atherosclerotic plaques in vivo. The method entails the use of monoclonal antibodies specific for activated platelets or activated endothelial cells. According to the method of this invention, a radiolabeled monoclonal antibody or antibody fragment specific for activated platelets, such as the monoclonal antibody S12 which is specific for the GMP-140 glycoprotein of activated platelets or activated endothelial cells, is administered to a patient suspected of having an endothelial injury such as an ulcerated atherosclerotic lesion. The radiolabeled monoclonal antibody is allowed to accumulate at the site of the plaque. Thereafter, the signal generated by the radiolabel is detected by a photoscanning device and the signal is converted to an image of the atherosclerotic plaque.

Detailed Description Text (3):
Preferred antibodies for plaque imaging are specific for an epitope of the GMP-140 protein, a marker of activated platelets. The protein is localized in alpha-granule membranes in unstimulated platelets. After thrombin stimulation and membrane fusion, the protein is redistributed to the cell surface and plasma membrane. The protein, GMP-140 has been described by Stenberg et al., J. Cell Biol., 101, 880 (1985).

Detailed Description Text (4):
In addition to being highly specific for activated platelets, antibodies specific for the GMP-140 glycoprotein have another advantage. The antibodies also react with endothelial GMP-140. Endothelial GMP-140, like its platelet counterpart, is localized to the membranes of secretory storage granules in unstimulated endothelial cells. When these cells are activated, the protein redistributes to the cell surface, just as it does in activated platelets. Thus, GMP-140 can serve a role as a

marker of activated endothelial cells damaged by atherosclerotic ulceration or other endothelial injury. Imaging methods of this invention employing platelet-specific monoclonal antibodies are able to detect sites of endothelial injury in which vascular lesions are associated with platelet activation. These ulcerated or ruptured sites of plaque formation can be detected using platelet-specific monoclonal antibodies.

Detailed Description Text (5):
A particularly preferred antibody for the method of this invention is the monoclonal antibody S12 which reacts specifically with the GMP-140 protein. The S12 antibody reacts minimally with unstimulated human platelets but binds extensively after platelets have been activated with thrombin. See McEver and Martin, J. Biol. Chem., 259:9799 (1984) incorporated herein by reference.

Detailed Description Text (6):
Antibodies against components of activated platelets other than GMP-140 may also be used. For example, the monoclonal antibody Tab, which binds to platelet glycoprotein IIb, can also be used in embodiments of this invention. See McEver et al., J. Biol. Chem., 258:5269 (1983), incorporated herein by reference.

Detailed Description Text (7):
GMP-140 specific monoclonal antibodies of this invention are produced by hybrid cell lines commonly known as hybridomas. These hybrid cells are formed by fusion of an anti-GMP-140 antibody.producing cell and an immortalizing partner (i.e. a cell line which imparts long term tissue culture stability to the hybrid cell). In the formation of the hybrid cell lines, the anti-GMP-140 antibody producing cell can be a B lymphocyte obtained from an animal or human who has developed an immune response to GMP-140: (i) naturally; (ii) as a result of a pathologic process; (iii) as a consequence of having been immunized with material containing GMP-140 such as activated platelets, activated endothelial cells, or a biological preparation comprising GMP-140. The immortalizing partner can be a cell of B lymphocyte lineage such as a B lymphoblastoid cell line or a plasmacytoma cell such as a myeloma cell, itself a antibody producing cell that is also malignant.

Detailed Description Text (8):
In particular, murine hybridomas producing GMP-140-specific monoclonal antibodies are formed by fusion of: (i) mouse myeloma cells and (ii) spleen cells from mice immunized against GMP-140 positive platelets or endothelial cells, purified GMP-140, or other biological preparations containing GMP-140. Fusions are accomplished by standard procedures well known in the art. Kohler and Milstein, Nature, 256, 495-497 (1975) and Kennet, Monoclonal Antibodies (Kennet et. al., eds.), pp. 365-367, Plenum Press. N.Y. 1980). The resulting murine hybridoma clones are then screened for production of antibody reactive with GMP-140-positive platelets, endothelial cells, or preparations containing GMP-140. Those which secrete antibodies of the appropriate reactivity and specificity are cloned to yield a homogeneous cell line secreting anti-GMP-140 antibody.

Detailed Description Text (12):
GMP-140 specific monoclonal antibodies are produced in large quantitities by injecting anti-GMP-140 antibody.producing hybridomas into the peritoneal cavity of mice or other appropriate hosts and, after appropriate time, harvesting the resulting ascitic fluid which contains a high titer of antibody, and isolating the desired anti-GMP-140 monoclonal antibody therefrom. Allogeneic or xenogeneic hybridomas can be injected into immunosuppressed, irradiated or athymic nude mice. Alternatively, the antibodies may be produced by culturing anti-GMP-140 producing cells in vitro and isolating secreted monoclonal anti-GMP-140 antibodies from the cell cuture medium.

Detailed Description Text (19):
The method of this invention can be used to distinguish between ulcerated and nonulcerated atherosclerotic plaque. The method is clinically useful for monitoring the extent of progression of atherosclerosis in heart attack survivors and in screening a population at risk for atherosclerosis (about 143 million worldwide). Information provided by the methods of this invention will aid physicians in evaluation of therapy and in early diagnosis of atherosclerotic plaque.

Detailed Description Text (35):
Rabbits weighing 5-10 lbs. received a 2% cholesterol atherogenic diet in order to elevate serum cholesterol levels. The diet consisted of rabbit chow supplemented by cholesterol-enriched peanut oil to produce hypercholesterolemia (cholesterol - 500-1000 mg %). This control group was kept on the diet for 1-2 weeks. A more severe atheroslcerotic condition was induced in the test group using the Baumgartner technique. Baumgartner H.R., Ges. Exp. Med. 137, 227, (1963). In brief, the endothelial lining of the infra.renal aorta is stripped or denuded by percutaneous placement of a 4 French Fogarty catheter via a femoral arteriotomy under sterile conditions. The catheter is retrogradely advanced through the iliac artery under fluoroscopic guidance. The balloon tip is inflated with saline and then drawn three times from the level of the renal to the proximal right iliac artery. After endothelial injury, the high cholesterol atherogenic diet is continued for an additional 4-6 weeks until the arterial re-injury phase of the study. This model has previously been shown to cause significant atherosclerosis characterized by intimal thickening, foam cell lesions and neovascularization in 66% of the animals. Baumgartner H.R., Ges. Exp. Med. 137,227 (1963).

Detailed Description Text (36):
B. Tc-99m Fab' Imaging of Arterial Injury in Rabbit Atherosclerosis Model

Detailed Description Text (37):
All rabbits were modeled to have atherosclerosis of the lower aorta and proximal iliac artery using a Fogarty catheter injury followed by high cholesterol diet for 4-6 weeks, as described previously. Rabbits were divided into three groups of increasingly severe aortic injury as follows:

Detailed Description Text (46):
A complete set of in vovo and ex vivo images, angiograms, x-rays and pathology pictures was taken from a rabbit that received a PTA stent following atherosclerotic modeling and previous Fogarty balloon injury. FIG. 2 shows a schematic diagram of the radiolocalization of the Tc-99m S12 Fab' in the descending aorta of this rabbit taken 35 minutes after injection. Localization is noted as the intense streak in the area of the descending aorta. Sixty minutes after imaging, the rabbit was sacrificed, the descending aorta was excised, washed free of blood and mounted for pathological examination. Visual analysis revealed a mixture of white and red thrombus in the wire mesh of the stent and extensive atherosclerosis over the entire region of the aorta. A representation of the ex vivo image of the excised aorta indicating the localization of the Tc-99m S12 Fab' is shown in FIG. 3. These data, taken together show an excellent correlation of the atherosclerotic injury site by angiography, pathology and in vivo and ex vivo imaging using the Tc-99m S12 Fab' antibody.

CLAIMS:

1. A method of imaging an atherosclerotic plaque, comprising the steps of:

a. administering to an individual suspected of having an atherosclerotic plaque, an effective amount of a radiolabeled monoclonal antibody or fragment thereof, specific for activated platelet or endothelial cell membrane protein GMP-140;

b. allowing the radiolabeled monoclonal antibody or antibody-fragment to accumulate at the plaque site;

c. detecting the signal generated by the radiolabel by means of a photoscanning device;

d. converting the detected signal into an image of the plaque.

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L5: Entry 1 of 94 File: USPT Jan 14, 2003

DOCUMENT-IDENTIFIER: US 6506382 B2
TITLE: Method for inhibiting reperfusion injury using antibodies to P-selectin glycoprotein ligand

Abstract Text (1):
P-selectin has been demonstrated to bind primarily to a single major glycoprotein ligand on neutrophils and HL-60 cells, when assessed by blotting assays and by affinity chromatography of [.sup.3 H]glucosamine-labeled HL-60 cell extracts on immobilized P-selectin. This molecule was characterized and distinguished from other well-characterized neutrophil membrane proteins with similar apparent molecular mass. The purified ligand, or fragments thereof (including both the carbohydrate and protein components), or antibodies to the ligand, or fragments thereof, can be used as inhibitors of binding of P-selectin to cells.

Brief Summary Text (11):
The purified ligand, or fragments thereof (including both the carbohydrate and protein components), or antibodies to the ligand, or fragments thereof, can be used as inhibitors of binding of P-selectin to cells.

Brief Summary Text (13):
U.S. Ser. No. 07/554,199 filed Jul. 17, 1990 entitled "Peptides Selectively Interacting with Selectins" by Rodger P. McEver, described the ability of P-selectin (GMP-140) to mediate cell-cell contact by binding to carbohydrate ligands on target cells and specific binding to protease-sensitive sites on human neutrophils. Studies with antibodies and with neuraminidase indicated that P-selectin bound to carbohydrate structures related to sialylated, fucosylated lactosaminoglycans. As described in U.S. Ser. No. 07/650,484 entitled "Ligand for GMP-140 Selectin and Methods of Use Thereof" filed Feb. 5, 1991 by Rodger P. McEver, P-selectin was also demonstrated to bind to sialylated, fucosylated lactosaminoglycans (including the tetrasaccharide sialyl Lewis x (sLe.sup.x)) on both myeloid and nonmyeloid cells.

Brief Summary Text (14):
The ability of proteases to abolish P-selectin binding to neutrophils indicated that high affinity binding of P-selectin to myeloid cells occurred through interactions with cell surface glycoprotein(s) rather than with glycolipids. As also described in U.S. Ser. No. 07/650,484, P-selectin bound preferentially to a glycoprotein in human neutrophil extracts of M.sub.r 120,000, as analyzed by SDS-PAGE under reducing conditions. The glycoprotein was partially purified on a P-selectin affinity column. It appeared to be heavily glycosylated because it stained poorly with silver and Coomassie blue. It appeared to be heavily sialylated because it bound to a wheat germ agglutinin affinity column. Treatment of the glycoprotein ligand with low doses of sialidase slowed its mobility on SDS gels, a pattern consistent with partial desialylation of heavily O-glycosylated proteins. Binding of P-selectin to the glycoprotein ligand was Ca.sup.2+ -dependent, blocked by monoclonal antibodies to P-selectin that also block P-selectin binding to leukocytes, and abolished by extensive treatment of the ligand with sialidase.

Brief Summary Text (16):
Further structural features of the glycoprotein ligand for P-selectin and a method for purifying the ligand are described below. The purified ligand, or fragments thereof (including both the carbohydrate and protein components), or antibodies to the ligand, or fragments thereof, can be used as inhibitors of binding of P-selectin to cells.

Detailed Description Text (5):
The anti-P-selectin murine mAbs S12 and G1, and goat anti-human P-selectin IgG were prepared and characterized as described by McEver and Martin, "A monoclonal antibody to a membrane glycoprotein binds only to activated platelets" J. Biol. Chem. 259:9799-9804 (1984); Geng et al., (1990); Lorant et al., (1991). Rabbit polyclonal antisera and murine mAbs to human lamp-1 (CD3), described by Carlsson et al., "Isolation and characterization of human lysosomal membrane glycoproteins, h-lamp-1 and h-lamp-2. Major sialoglycoproteins carrying polylactosaminoglycan" J. Biol. Chem. 263:18911-18919 (1988), and lamp-2 (BB6), Carlsson and Fukuda, "Structure of human lysosomal membrane glycoprotein 1. Assignment of disulfide bonds and visualization of its domain arrangment" J. Biol. Chem. 264:20526-20531 (1989), and rabbit polyclonal anti-human leukosialin antiserum, described by Carlsson and Fukuda, "Isolation and characterization of leukosialin, a major sialoglycoprotein on human leukocytes" J. Biol. Chem. 261:12779-12786 (1986) were provided by Dr. Sven Carlsson (University of Umea, Umea, Sweden). Anti-human leukosialin (CD43) mAb (Leu-22) was purchased from Becton Dickinson & Co. (San Jose, Calif.). The anti-L-selectin murine mAb antibodies DREG-56, DREG-55, and DREG-200, described by Kishimoto et al., "Identification of a human peripheral lymph node receptor: a rapidly down-regulated adhesion receptor" Proc. Natl. Acad. Sci. USA 87:2244-2248 (1990) were provided by Dr. Takashi Kei Kishimoto (Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Conn.). All mAbs are of the IgG.sub.1 subtype and were used in purified form. Leukosialin purified from HL 60 cells (Carlsson and Fukuda, 1986) was provided by Dr. Sven Carlsson (University of Umea). P-selectin was purified from human platelets as described by Moore et al., (1991). The teachings of these references are specifically incorporated herein.

Detailed Description Text (23):
Human neutrophils, isolated as described by Hamburger and McEver, (1990), were suspended (10.sup.6 /ml) in HBSS containing 1% FCS and 0.1% sodium azide (HBSS/FCS/Az). 1 ml of neutrophil suspension was underlaid with 100 .mu.l FCS and centrifuged at 500 g for 5 min. The neutrophil pellet was resuspended in 50 .mu.l of purified P selectin (10 .mu.l/ml, in HBSS/FCS/Az), and then incubated sequentially with 50 .mu.l of biotin-conjugated S12 (10 .mu.g/ml, in HBSS/FCS/Az) and 20 .mu.l of phycoerythrin-streptavidin (neat). In certain experiments, the neutrophils were preincubated for 10-15 min with antisera or antibodies before the addition of P-selectin. Between each step the cells were diluted with one ml of HBSS/FCS/Az, underlaid with 100 .mu.l FCS, and centrifuged at 500 g for 5 min. All steps were performed at 4.degree. C. After the last wash, the cells were fixed with 1 ml of 1% paraformaldehyde in HBSS and analyzed in a FACScan flow cytometer (FACScan is a registered trademark of Becton Dickinson & Co., Mountain View, Calif.) formatted for two color analysis as described by Moore, et al., (1991). Binding of P-selectin to intact neutrophils as assessed by this assay was Ca.sup.2+ -dependent, was blocked by G1, and was abolished by pretreatment of the cells with trypsin or sialidase.

Detailed Description Text (25):
WGA eluate was incubated with 10 .mu.g of anti-leukosialin (Leu22) or an isotype matched control monoclonal antibody for 1 h at 37.degree. C. The mixture was then incubated with protein A-Sepharose CL4B beads saturated with rabbit anti-mouse IgG for 1 h at 37.degree. C. The beads were pelleted, washed four times with 1 ml of 0.1 M NaCl, 20 mM Tris, pH 7.5, 1% Triton X-100, and bound material eluted by boiling 5 min in 2% SDS, 60 mM Tris, pH 6.8, and 5% .beta.-mercaptoethanol. Immunoprecipitates and immunosupernatants were then analyzed by P-selectin blotting and by Western blotting using Leu22 as a probe.

Detailed Description Text (46):
Membrane extracts (200 .mu.g protein/lane) were electrophoresed on 7.5% SDS-polyacrylamide gels under nonreducing or reducing conditions, transferred to Immobilon membranes, and probed with [.sup.125 I]P-selectin or murine monoclonal antibodies directed against human lamp-1 (CR3), human lamp-2 (BB6), human L-selectin (DREG-200), or human leukosialin (Leu22). Western blot analysis of neutrophil membranes with mAbs to lamp-1 and lamp-2 showed that the electrophoretic mobilities of these proteins under nonreducing conditions were distinct from that of the P-selectin ligand. In contrast to the P-selectin ligand, the electrophoretic mobilities of lamp-1 and lamp-2 are not affected by sialidase treatment. Although

lamp-1 and lamp-2 from myeloid cells are rich in lactosaminoglycans sensitive to endo-.beta.-galactosidase, treatment of intact neutrophils with the enzyme did not affect binding of [.sup.125 I]P-selectin. Pretreatment of crude neutrophil membrane extracts or WGA column eluate with endo .beta.-galactosidase (200 mU/ml, 1-2 h, 37.degree. C.) also did not affect the apparent molecular weight of the ligand or its ability to bind [.sup.125 I]P-selectin. These data argue that lamp-1 and lamp-2 are not ligands for P-selectin even though they carry many sialyl Le.sup.x structures.

Detailed Description Text (47):
The third molecule whose apparent molecular weight is similar to the 120,000 D P-selectin ligand is CD43 (leukosialin, sialophorin), a heavily sialylated membrane protein present on platelets and all leukocytes. It carries numerous O-linked sugar chains and is differentially glycosylated by cells of various hematopoietic lineages. Like the P-selectin ligand, treatment of leukosialin with sialidase increases its apparent molecular weight. However, in contrast to the P-selectin ligand, the electrophoretic mobility of leukosialin was unaffected by reduction. Monospecific polyclonal anti-human leukosialin antisera (1:5 dilution) did not inhibit P-selectin binding to neutrophils as assessed by flow cytometry. Furthermore, immunodepletion of leukosialin from neutrophil membrane extracts did not deplete P-selectin ligand as assessed by the blotting assay. Finally, leukosialin purified from HL-60 cells did not bind P-selectin. Neutrophil WGA eluate (50 .mu.g) and leukosialin purified from HL-60 cells (0.5 .mu.g) were electrophoresed under reducing conditions on 7.5% SDS-polyacrylamide gels, transferred to Immobilon, and probed with [.sup.125 I]P-selectin. The same membrane was then probed with the monocional anti-human leukosialin antibody Leu22.

Detailed Description Text (48):
Based on studies in which an antibody to L-selectin (DREG-56) partially inhibited neutrophil adhesion to P-selectin-transfected cells, it was suggested that L-selectin is an important glycoprotein ligand on myeloid cells for P-selectin by Picker et al., "The neutrophil selectin LECAM-1 presents carbohydrate ligands to the vascular selectins ELAM-1 and GMP-140" Cell 66:921-933 (1991). Although L-selectin is present in membrane extracts and WGA eluates of neutrophil membranes, as detected by Western blotting, [.sup.125 I]P-selectin did not bind to L-selectin in the blotting assay. In addition, the anti-L-selectin mAb DREG-56 (100 .mu.g/ml) had no effect on the binding of purified P-selectin to quiescent neutrophils as assessed by flow cytometry. Neutrophils were preincubated for 15 min with buffer alone, 100 .mu./ml of the anti-L-selectin monoclonal antibody DREG-56, or 100 .mu.g/ml of the anti-P-selectin mAb GI before addition of buffer or P-selectin. P-selectin binding was then detected by sequential incubation of the cells with biotinylated S12 (a noninhibitory monoclonal antibody to P-selectin) and phycoerythrin-streptavidin as described in Materials and Methods.

Detailed Description Text (49):
Parallel control assays showed that the neutrophils expressed high levels of L-selectin detactable by DREG-56. Binding of the anti-L-selectin mAb DREG-56 to the neutrophils was assessed by indirect immunofluorescence using a phycoerythrin-conjugated anti-murine IgG.sub.1 antibody. Identical results were obtained with the anti-L-selectin mAbs DREG-55 and DREG-200. Thus, interactions with L-selectin do not appear to contribute to the binding of fluid-phase P-selectin to intact neutrophils or to immobilized proteins from neutrophil membrane extracts.

Detailed Description Text (56):
The ligand contains the sialyl Lewis x (SLe.sup.x) antigen (NeuAca2-3Gal.beta.1-4 [Fuca1-3]GlcNAc.beta.-R). When the .sup.3 H-glucosamine-labeled P-selectin ligand from HL-60 cells was reapplied to a column of P-selectin-Affigel.TM.-15 it rebound. When this chromatography was done in the presence of antibody to the SLe.sup.x antigen (CSLEX1 monoclonal antibody (Fukushima, et al., Cancer Res. 44:5279-5285, 1984)), purchased from Dr. Paul Teraski, University of California at Los Angeles, binding was more than 90% reduced. In contrast, when a control experiment was done in which the rechromatography occurred in the presence of antibody to the Le.sup.x antigen (which lacks sialic acid), there was little if any effect. The CSLEX1 anti-SLe.sup.x antibody bound to the ligand as assessed by Western blotting.

Detailed Description Text (62):
It has been demonstrated that L-selectin on neutrophils carries the sialyl Le.sup.x epitope and that a mAb to L-selectin partially blocks neutrophil adhesion to cells transfected with P-selectin cDNA (Picker, it al., Cell 66:921-933, 1991). Based on these observations, it was proposed that L-selectin on neutrophils is a predominant ligand for P-selectin. However, no direct interaction of L-selectin with P-selectin was demonstrated. In the present study, binding of P-selectin to L-selectin in neutrophil membrane extracts was not detectable. Furthermore, the binding of P-selectin to intact neutrophils is unaltered by antibodies to L-selectin or by neutrophil activation that causes shedding of L-selectin from the cell surface. Although it is conceivable that L-selectin has weak affinity for P-selectin, the significance of this potential interaction remains to be established.

Detailed Description Text (72):
Antibodies to the ligand can be used for the detection of human disorders in which P-selectin ligands might be defective. Such disorders would most likely be seen in patients with increased susceptibility to infections in which leukocytes might not be able to bind to activated platelets or endothelium. Cells to be tested, usually leukocytes, are collected by standard medically approved techniques and screened. Detection systems include ELISA procedures, binding of radiolabeled antibody to immobilized activated cells, flow cytometry, immunoperoxidase or immunogold analysis, or other methods known to those skilled in the arts.

Detailed Description Text (73):
Antibodies directed specifically to protein or carbohydrate components of the ligand can be use to distinquish defects in expression of the core protein or in glycosyltransferases and/or modifying enzymes that construct the proper oligosaccharide chains on the protein. The antibodies can also be used to screen cells and tissues other than leukocytes for expression of the protein or carbohydrate components of the ligand for P-selectin. Complementary DNA clones encoding the protein component of the ligand can be isolated and sequenced. These probes can be used as diagnostic reagents to examine expression of RNA transcripts for the ligand in leukocytes and other tissues by standard procedures such as Northern blotting of RNA isolated from cells and in situ hybridization of tissue sections.

Detailed Description Text (77):
Since P-selectin has several functions related to leukocyte adherence, inflammation, tumor metastases, and coagulation, clinically, compounds which interfere with binding of P-selectin and/or the other selecting, including E-selectin and L-selectin, such as the carbohydrates, can be used to modulate these responses. These compounds include the P-selectin ligand, antibodies to the ligand, and fragments thereof. For example, the glycoprotein ligand, or components thereof, particularly the carbohydrate moieties, can be use to inhibit leukocyte adhesion by competitively binding to P-selectin expressed on the surface of activated platelets or endothelial cells. Similarly, antibodies to the ligand can be used to block cell adhesion mediated by P-selectin by competively binding to the P-selectin ligand on leukocytes or other cells. These therapies are useful in acute situations where effective, but transient, inhibition of leukocyte-mediated inflammation is desirable. In addition, treatment of chronic disorders may be attained by sustained administration of agents, for example, by subcutaneous or oral administration.

Detailed Description Text (78):
An inflammatory response may cause damage to the host if unchecked, because leukocytes release many toxic molecules that can damage normal tissues. These molecules include proteolytic enzymes and free radicals. Examples of pathological situations in which leukocytes can cause tissue damage include injury from ischemia and reperfusion, bacterial sepsis and disseminated intravascular coagulation, adult respiratory distress syndrome, tumor metastasis, rheumatoid arthritis and atherosclerosis.

Detailed Description Text (85):
Platelet-leukocyte interactions are believed to be important in atherosclerosis. Platelets might have a role in recruitment of monocytes into atherosclerotic plaques; the accumulation of monocytes is known to be one of the earliest detectable

events during atherogenesis. Rupture of a fully developed plaque may not only lead to platelet deposition and activation and the promotion of thrombus formation, but also the early recruitment of neutrophils to an area of ischemia.

Detailed Description Text (87):
In these clinical applications, the glycoprotein ligand, or fragments thereof, can be administered to block selectin-dependent interactions by binding competitively to P-selectin expressed on activated cells. In particular, carbohydrate components of the ligand, which play a key role in recognition by P-selectin, can be administered. Similarly, natural or synthetic analogs of the ligand or its fragments which bind to P-selectin can also be administered. In addition, antibodies to the protein and/or carbohydrate components of the ligand, or fragments thereof, can be administered. The antibodies are preferably of human origin or modified to delete those portions most likely to cause an immunogenic reaction. Carbohydrate components of the ligand or the antibodies, in an appropriate pharmaceutical carrier,; are preferably administered intravenously where immediate relief is required. The carbohydrate(s) can also be administered intramuscularly, intraperitoneally, subcutaneously, orally, as the carbohydrate, conjugated to a carrier molecule, or in a drug delivery device. The carbohydrate can be modified chemically to increase its in vivo half-life.

Detailed Description Text (94):
Modifications and variations of the present invention, methods for modulating binding reactions involving P-selectin using carbohydrate derived from or forming a portion of the P-selectin ligand, or antibodies to the ligand, will be obvious to those skilled in the art from the foregoing detailed description. Such modifications and variations are intended to come within the scope of the appended claims.

Other Reference Publication (140):
Winn et al., "Monoclonal Antibodies to P-Selectin Are Effective in Preventing Reperfusion Injury to Rabbit Ears", Supplement I Circulation, 86(4):0316 (1992).

CLAIMS:

1. A method for inhibiting reperfusion injury comprising administering an effective amount of an antibody to a protein component or to a carbohydrate-protein component of P-selectin glycoprotein ligand, the glycoprotein ligand comprising a fucosylated sialylated glycoprotein containing sialyl Lewis.sup.x antigen and the glycoprotein ligand having an apparent relative molecular weight of 120,000 as assessed by SDS-PAGE under reducing conditions and wherein the antibody has binding specific for P-selectin glycoprotein ligand and wherein the antibody inhibits binding of P-selectin glycoprotein ligand to P-selectin.

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